REMARKS

Status of the Claims

Claims 1-7, 9-24, and 26-29 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,017,693 ("Yates") in view of U.S. Patent No. 5,710,213 ("Wright") and the article "*Improving protein identification from peptide mass fingerprinting through a parameterized multi-level scoring algorithm and optimized peak detection*" in Electrophoresis 1999, Volume 20, pages 3535-3550 by Gras, et al. ("Gras") (collectively "the cited references"). Applicant hereby amends claim 23. After entry of this paper, claims 1-7, 9-24, and 26-29 remain pending for examination.

Amendments to the Claims

Applicant hereby amends claim 23. Support for the amendments to claim 23 is found at least at page 3, lines 15-16 and 24-26; page 19, line 21 to page 21, line 4; page 33, line 28 to page 34, line 1; and original claim 25. Accordingly, the amendments to claim 23 add no new matter.

Rejections Under 35 U.S.C §103

Claims 1-7, 9-24, and 26-29 were rejected under U.S.C. §103 as allegedly obvious over Yates in view of Wright. Applicant notes that although Wright is cited as a basis for the rejections, the Final Action points to no portion of Wright as teaching or suggesting any portion of Applicant's claims or the combination of Yates and Gras. Accordingly, Applicant believes that the Wright reference does not form a part of the rejections currently being applied.

Applicant submits that the cited references, either alone or in combination, fail to teach or suggest all elements of Applicant's claims, or these claims as a whole. The cited references do not teach or suggest "determining a biomolecule fragment score" of a mass signal using, *inter alia*, a mass signal intensity, a biomolecule fragment detection parameter, and a mass error for the mass signal, as set forth in Applicant's claims. Accordingly, Applicant submits the Final Office Action fails to establish a *prima facie* case of obviousness against the pending claims.

Specifically, Applicant's independent claims 1 and 23, each require a step of:

> determining a biomolecule fragment score for said mass signal, wherein said biomolecule fragment score comprises a function of:
>
> the mass signal intensity for said mass signal,
>
> a biomolecule fragment detection parameter for a biomolecule fragment of said potential source biomolecule, said biological fragment detection parameter for said biomolecule fragment comprises a numerical value that is a measure of the likelihood of detecting the biomolecule fragment as a fragment, digestion product, or both, of said potential source biomolecule, the likelihood of detecting said biological fragment being based at least in part on relative mass signal intensity relationships between biomolecule fragments, fractions of biomolecule fragments, or both; and
>
> a mass error for said mass signal from the relative difference between a mass which corresponds to said mass signal and a mass of the biomolecule fragment;

(emphasis added). Applicant submits that the Final Office Action has failed to show how the cited references teach or suggest, either alone or in combination, the above quoted determining step or the claims as a whole. In particular, the Final Office Action has failed to show where the cited references teach or suggest a "biomolecule fragment detection parameter" as that term is used in the claims.

In particular, the specification (for example, at page 2, lines 22-26) makes clear to one of ordinary skill in the art that the "biomolecule fragment detection parameter,"

> [takes] into account the likelihood of detecting a biomolecule fragment as a mass signal in the mass spectrum of the sample. The numerical value associated with the likelihood of detecting a biomolecule fragment from a given biomolecule is referred to as a "biomolecule fragment detection parameter."

(emphasis added, quotations in original). The specification further describes (for example at page 21, line 30, to page 30, line 5) that

> the numerical values of the [biomolecule fragment detection] parameters reflect the general relative mass signal intensity relationships between biomolecule fragments, and/or the fraction of a biomolecule fragment generally observed, in a mass spectrum of the sample or related samples that arise from differences in biomolecule fragment sequence and chemistry of the biomolecule fragmentation and/or digestion

(emphasis added) and describe (for example, at page 30, lines 10-20) how the general intensity relationships can be determined:

> The general relative intensity relationship can be determined by comparison of measured biomolecule fragment mass signal intensities generated from a sample of known biomolecule(s). Alternatively, the general relative intensity relationship can be determined from comparison of biomolecule fragment mass signal intensities predicted for a sample. ... The relative intensity relationship and fraction of a biomolecule fragment generally observed may be determined, for example, from published data or from data obtained by the investigator. An example of the latter such determination is illustrated below in Example 1 for an analysis employing a trypsin digest of proteins and a MALDI-TOF mass spectrometry technique.

(emphasis added).

For example, a biomolecule fragment detection parameter can be determined by comparison of measured biomolecule fragment mass signal intensities generated from a sample of known biomolecules. For example, if a known sample of biomolecules contain a concentration X of peptide A, and the measured intensity of the mass signal for A in a mass spectrum of the known sample corresponds to a concentration Y; the relative intensity relationship in this example is X/Y.

Accordingly, the specification makes clear that a biomolecule fragment detection parameter, of the present invention, reflects the general relative mass signal intensity relationships that arise from differences in the likelihood of detecting different biomolecule fragments as a mass signal in the mass spectrum of the sample.

Applicant reads the Final Action as stating (pages 2-3) that the element of a "biomolecule fragment detection parameter" is not found in Yates but rather in Gras. Applicant agrees that Yates does not teach or suggest using mass signal intensity to determine either a "biomolecule fragment score" or a "biological fragment detection parameter" as set forth in the claims.

Applicant, however, disagrees with the position that Gras teaches or suggests a "biomolecule fragment score" that is a function of a "biological fragment detection parameter" as set forth in Applicant's claims. The Final Action states at page 3 (emphasis added):

> Gras et al teaches the calculation of an "identification score"...and defines the parameters for the scoring function in Section 2.4.3.2...This was pointed to on page 6, lines 11-13 in the Office Action of April 22, 2005....The limitation in claim 1 recites that a biomolecule fragment score comprises a function of a biomolecule fragment detection parameter which is the "likelihood of detecting said biomolecule fragment...based at least in

> part on relative mass signal intensity relationships." Gras et al. also uses, in part, the intensity of peaks to determine a score for matching searched protein and candidate proteins through peptide mass fingerprinting.

The Final Action, however, fails to show how Gras's use of peak intensity to determine a score provides, teaches or suggests "the likelihood of detecting said biological fragment being based at least in part on relative mass signal intensity relationships between biomolecule fragments, fractions of biomolecule fragments, or both" for a biomolecule fragment. Rather, for a given mass signal (peak), Gras only uses the intensity of that peak in his "score" for that peak.

Specifically, in the terminology of Gras, at the "mass level" or "level 1" (see, e.g., Gras at page 3542, section 2.4.3.2) for a given peak (e.g., peptide mass) Gras uses only "the intensity of the corresponding peak in the mass spectrum," $coef_i(a)$, to calculate a score at this level. Gras does not teach or suggest using relative mass signal intensity relationships in calculating a score for a given biomolecule fragment such as a peptide. As a result, the Final Action's assertion that Gras' use of signal intensity teaches use of relative mass signal intensity relationships as set forth in the clams is incorrect; no relative intensity relationship is ever used in determining a score.

To the extent the Final Office Action asserts that because Gras uses mass signal intensity that this is equitable to relative mass signal intensity relationships; this is simply not the case and takes Gras out of context. Further, asserting that Gras uses mass signal intensities and Applicant uses mass signal intensities is not the end of the analysis of the patentability of Applicant's claims and does not show how Gras uses, teaches or suggests relative mass signal intensity relationships as set forth in Applicant's claims. Accordingly, the Final Action does not establish that the element of a "biomolecule fragment detection parameter" as used in the claims is taught by the cited references, either alone or in combination.

Gras' use of such parameters as number of chemical modifications, and number of missed cleavages and their associated coefficients also do not provide a "biomolecule fragment detection parameter" based at least in part on relative mass signal intensity relationships as set forth in Applicant's claims, and Applicant does not believe the Final Action asserts otherwise. Nevertheless, Applicant notes that Gras uses the parameters of number of chemical modifications, and number of missed cleavages to determine the confidence of a match:

> At the mass level, the first goal is to determine the quality of a peak, that is to determine when a peak may be considered a "true" peak. For that purpose...[a] level of confidence is also defined for the match of an experimental mass with a theoretical mass...with the help of parameters such as the number of modifications, the number of missed cleavages necessary for the match...

(Gras at page 3541, 2nd column, last paragraph). Thus, Gras teaches and uses the chemical modifications and missed cleavages parameters as a measure of matching tolerance based on mass not relative mass signal intensity relationships. In the field of mass spectrometric analysis, mass difference is distinctly different from and not equatable with the signal intensity associated with a mass signal. As a result, mass error, matching or confidence levels based on mass differences do not take into account the likelihood of detecting a peptide as a mass signal in the mass spectrum of a sample containing that peptide or reflect general relative mass signal intensity relationships. Accordingly, the parameters of number of chemical modifications and number of missed cleavages as taught by Gras cannot be interpreted as a "biomolecule fragment detection parameter" as this term is used in Applicant's claims.

Applicant does not understand the statements in the Final Action at pages 3-4 with respect to "mass level...which corresponds to the mass error" or the "level 2" or protein level parameters of Gras that "include the confidence level for the match" based on comparing experimental and theoretical masses of the protein, to assert that either one of these can be equated to a "biological fragment detection parameter" as set forth in Applicant's claims for determining a "biomolecule fragment score"; but to the extent such may be asserted, Applicant must disagree for the reasons set forth above that mass difference or confidence level parameters based on mass, as taught in the cited references, cannot be interpreted as a "biomolecule fragment detection parameter" to determine a "biomolecule fragment score" as those terms are used in Applicant's claims.

For the reasons stated above, Applicant does not believe Wright forms a basis for the present rejections. Nevertheless, Applicant submits that Wright, either alone or in combination with Gras and/or Yates, does not provide the teachings missing in Yates and Gras of a "biomolecule fragment detection parameter" as set forth in Applicant's claims.

The "determining a biomolecule fragment score" step is a specific step of Applicant's method claims that must be taught by the cited references to render Applicant's claims obvious.

The "biomolecule fragment score" of a mass signal is further limited as being determined from, *inter alia*, a biomolecule fragment detection parameter for said mass signal based, at least in part, on relative mass signal intensity relationships between biomolecule fragments (and/or fractions thereof). Accordingly, as the Final Action has failed to show where the cited references teach or suggest determining a biomolecule fragment detection parameter using at least in part relative mass signal intensity relationships, Applicant submits that the Final Action has failed to establish a *prima facie* case of obviousness against Applicant's claims. In view of the above, it is believed that all presently pending claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

CONCLUSION

In view of the above, it is believed that all presently pending claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone call would expedite the prosecution of this case, the Examiner is invited to call the undersigned at (617) 248-5000.

Applicant believes that no additional fee is due with this amendment and Reply. However, if any additional fee is due, please charge our Deposit Account 50-1191, under Order No. SY9-155 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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